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10/700,158	11/03/2003	Ting-Fen Tsai	5223-4	3816

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EXAMINER	
ALONZO, NORMA LYN	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,158	TSAI ET AL.	
	Examiner	Art Unit	
	Norma C Alonzo	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 03 November 2003 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 1/8/04.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-8 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for (i) a transgenic mouse whose somatic and germ cells comprising a vector, wherein said vector comprises: a first transgene expression cassette comprising mouse agouti cDNA operably linked to a human keratinocyte specific K14 promoter (K14-Ag), a second transgene expression cassette comprising RNA polymerase II large subunit promoter, and a chicken beta-globulin HS4 insulator, wherein said insulator and said first expression cassette are located at the 5' or 3' end of said second transgene expression cassette, wherein the number of copies of said chicken beta-globin HS4 insulator is 1-6, wherein said insulator is in the same or opposite orientation relative to said first and second expression cassettes in said vector (ii) a method of producing said transgenic mouse comprising (a) introducing said vector into a mouse embryo or a mouse ES cell and transferring said ES cell into a zygote, (b) transferring said embryo or said zygote comprising said ES cell into a pseudopregnant

female mouse, allowing said embryo or zygote to develop into an offspring, and selecting an offspring that expresses said agouti cDNA and has a coat color phenotype and (iii) said vector, does not reasonably provide enablement for a transgenic mouse comprising any agouti cDNA. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make and use the claimed invention, if not, whether an artisan would have required undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue" (In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400 , 1404 (Fed. Cir. 1988)). Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of the invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The breadth of the claims encompasses a vector comprising a dominant coat color transgene, a transgene expression cassette and an insulator, a transgenic mouse produced by using said vector and a method for using said mouse for identifying a genotype of a transgenic mouse and reducing the variability of a transgene expression in said transgenic mouse. The nature of the invention is to a transgenic mouse, a composition used to make said mouse and a method for using said mouse. The claims are drawn to a transgenic mouse wherein said mouse was made by a method of microinjecting a vector comprising a K14-Ag expression cassette, a RNA polymerase II large subunit promoter transgene cassette and a chicken beta-globin HS4 insulator. Whereas the disclosure teaches an expression cassette comprising the mouse agouti cDNA operably linked to the human K14 promoter, the claims are drawn to any expression cassette comprising any agouti cDNA operably linked to the K14 promoter to produce a transgenic mouse.

The art of transgenic animals has for many years stated that unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have, within their cells, cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the geneome (Kappel, et al. (1992) Current Opinion in Biotechnology, 3: 549, col. 2, paragraph 2). Mullins et al. (1993) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins, et al. (1993) Hypertension 22, page 631, col. 1, paragraph 1, lines 14-17). The elements of the

particular construct used to make the transgenic animal are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene, e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) J. Biotech., 34, page 281). "The position effect" and unidentified control elements also are recognized to cause abberant expression (Wall (1996) Theriogenology 45, page 61, paragraph 2, line 9 to page 62, line 3). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997) Molec. Biol., 7, page 256, lines 10-13). Further, Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus, the phenotype observed (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, paragraph 1, lines 1-7). With regard to the import of promoter selection, Niemann states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes - one deleterious to, the other compatible with, pig health (Niemann (1997) Transg. Res. 7, page 73, col. 2).

Further, wherein the agouti gene is found in most animal species, the phylogenetic disparity between mice and humans would be reflected in a potential difference in function of the mouse agouti gene versus the human agouti gene in light of the state of the art of animal transgenesis. Therefore, in order for a skilled artisan to be enabled for the full scope of the claimed embodiment, a method of making a transgenic mouse comprising a vector comprising an agouti gene operably linked to a K14

promoter, a skilled artisan would have to be able to make a transgenic mouse comprising a vector comprising a canine agouti gene or a porcine agouti gene that can be used in a method of identifying a genotype of a transgenic mouse and reducing the variability of a transgene expression in said transgenic mouse.

Though it is known in the art that agouti exists in many animal species, including "animals of the genera *Mus* (mouse), *Oryctolagus* (rabbits), *Sciurus* (squirrels), and *Canis* (wolves)," (page 4721, paragraph 1, Manne et al. Proc Natl Acad Sci 92:4721-4724, 1995) as well as porcine (see Abstract, Wang et al. Pigment Cell Res 11(3):155-157, 1998), it is not well known in the art the level of conserved homology that exists between the different agouti genes of non-similar animal species. Therefore, in view of the state of the art of animal transgenesis and the embodiment of the claimed invention encompassing a vector comprising any agouti transgene and while the level of skill of an artisan practicing the claimed invention will be high, in view of the unpredictability of the state of the art, an artisan would require specific guidance to carry out the full breadth of the claimed invention.

The instant specification broadly discusses the embodiments of the claimed invention wherein a transgenic mouse could be made having cells comprising multiple transgenes using a vector having a K14-Ag expression cassette, a transgene expression cassette having a different promoter and a chicken beta-globin HS4 insulator. The instant specification further teaches a working example wherein a transgenic mouse is produced wherein a vector comprising an expression cassette comprising the mouse agouti gene operably linked to the human K14 promoter, an

expression cassette comprising RNA polymerase II large subunit promoter and a chicken beta-globin HS4 insulator. The authors further teach positional variations of said insulator and K14-Ag wherein the progeny resulting from transgenesis of vectors produced by these positional variations exhibit predicted phenotypes of mottled to yellow coats. Finally, the authors teach a method of identifying the genotype of said mice and selecting said mice for transgenesis. However, the instant specification does not teach the method of making a transgenic mouse using a vector comprising an expression cassette having any mouse agouti gene other than mouse operably linked to the human K14 promoter. In view of the unpredictability of the art of transgenesis and further in view of the existence of species-specific agouti genes, a skilled artisan is not enabled to make and use a mouse using a vector comprising an expression cassette having any agouti gene without specific guidance provided by the instant specification. Lacking this specific guidance from the instant specification and in view of the unpredictability of the art of animal transgenesis, it would take a undue quantity of necessary experimentation to make or use the full embodiment of the claimed invention, a mouse made by a method comprising a vector having any K14-Ag expression cassette, a transgene expression cassette having RNA polymerase II large subunit promoter, and a chicken beta-globin HS4 insulator and a method of using said mouse comprising selecting a mouse for transgenesis by visually detecting a phenotype exhibiting coat color as a result of the integration of the three transgenes found in said cassette into the genome of said transgenic animal.

Therefore, in view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the claimed invention is not enabled for its full breadth and limiting the scope of the claimed invention to (i) a transgenic mouse whose somatic and germ cells comprise a vector comprising a vector comprising mouse agouti cDNA operably linked to human keratinocyte specific K14 promoter (K14-Ag), a transgene expression cassette having RNA polymerase II large subunit promoter, and a chicken beta-globulin HS4 insulator wherein said insulator and said K14-Ag are located at the 5' or 3' end of said transgene expression cassette wherein the number of copies of said chicken beta-globin HS4 insulator is 1-6 wherein said insulator has the same or opposite orientation relative to said transgene expression cassette and said K14-Ag in said vector (ii) a method of using said mouse comprising introducing said vector into a mouse embryo, or introducing said vector into a mouse ES cell and transferring said ES cell into a zygote, transferring said embryo or said zygote into a pseudopregnant female mouse, allowing said embryo or zygote to develop into offspring, and selecting an offspring for transgenesis by visually detecting a coat color phenotype and (iii) said vector is proper.

3. Claims 1-8 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to

one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claim(s) 1-8 encompasses a dominant coat color marker.

The dominant coat color marker of these claim(s) are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses a vector comprising an expression cassette comprising a mouse agouti cDNA operably linked to a K14 keratin promoter, a transgenic mouse produced by a method comprising said vector and a method of using said mouse to identify a genotype of a transgenic mouse and reducing the variability of a transgene expression in said transgenic mouse.

In analyzing whether the written description requirement is met for gene claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, the instant specification discloses only one dominant coat color marker, the K14-Ag expression cassette wherein said cassette comprises a mouse agouti cDNA driven by the keratinocyte specific K14 promoter. Integration of said expression cassette in conjunction with the transgene expression cassette having RNA polymerase II large subunit promoter, and a chicken beta-globin HS4 insulator, produced transgenic mice having the yellow coat color phenotype. However, the specification does not describe any other dominant coat color marker. The specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have

been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only specific feature or functional attribute described by the instant specification for a dominant coat color marker is the resulting coat color phenotype expressed in the transgenic mouse as a result of the transgenesis of the vector comprising the K14-Ag cassette. However, the instant specification does not describe the coat color phenotype that would have been expressed in a transgenic mouse having cells comprising any coat color marker other than K14-Ag.

The lack of such functional characteristics does not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any dominant coat color marker,

at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1 and 7-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 8 cite the term "identifying a genotype of a transgenic mouse." Wherein the method steps further recite "a phenotype exhibiting coat color, it is unclear how any other genotype of a transgenic mouse could be identified by the claimed method.

Claim 1, step (a) recites the term "a vector comprising a dominant coat marker." The claim is indefinite because it is not clear how a vector can comprise a marker, which is a protein. A vector can comprise a nucleic acid encoding a marker, but cannot comprise the marker itself.

Claims 1, step (a), and 7 recite the term "introducing into the genome of a mouse a vector." The claims are indefinite because it is not clear how a vector could be introduced into the genome of a mouse.

Claim 1, step (b), recites the term "resulting from said expression cassette K14-Ag." This claim is indefinite because it is not clear how an expression cassette can produce a coat color phenotype without an active method step.

Claim 8 recites the term "a vector for identifying a genotype of a transgenic mouse." The claim is indefinite because it is not clear how a vector can identify a genotype of a transgenic mouse. A vector without a mouse and without active method steps cannot identify a genotype of a transgenic mouse.

Conclusion

4. No claims are allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Norma C Alonzo whose telephone number is 571-272-2910. The examiner can normally be reached on 8-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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